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Animal Drug User Fee Programs

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Summary

The Animal Drug User Fee Act of 2003 (ADUFA I, P.L. 108-130) gave the Food and Drug Administration (FDA) initial authority to collect user fees from sponsors for the review of animal drug applications. ADUFA mirrors fee programs for human drugs and medical devices. Program authority sunsets October 1, 2008, and FDA would have to lay off staff in its review program if the program were not reauthorized by then. ADUFA supporters—including companies that make brand-name animal drugs, and livestock producer groups—considered ADUFA reauthorization to be “must pass” legislation in the 110th Congress. A coalition of consumer groups opposed the program and its reauthorization, citing, in particular, concerns about the safety of animal drugs used in livestock production.

After negotiations with brand-name animal drug companies, FDA made several proposals for the reauthorization of ADUFA (ADUFA II), including a near-doubling of the total amount of fees to be collected in the future. The proposed increase would support continued enhancements of FDA’s review program, further improvements in the timeliness of reviews, and the elimination of a backlog of pre-approval inspections of foreign manufacturing facilities. FDA presented draft reauthorizing legislation to Congress in April 2008. **H.R. 6432**, the Animal Drug User Fee Amendments of 2008, a bill to reauthorize the program, was introduced on July 8, 2008. Subsequently, the bill was forwarded without amendment to the full committee by the House Energy and Commerce Subcommittee on Health, and was marked up by the full committee on July 16, 2008.

ADUFA does not cover generic animal drugs. FDA has not been able to maintain the statutory requirement for timeliness of generic animal drug reviews since ADUFA was enacted. FDA presented a draft Animal Generic Drug User Fee Act (AGDUFA) to Congress in April 2008, separate from the ADUFA II draft bill. **H.R. 6433**, the Animal Generic Drug User Fee Act of 2008, was introduced on July 8, 2008. Subsequently, the bill was forwarded without amendment to the full committee by the House Energy and Commerce Subcommittee on Health, and was marked up by the full committee on July 16, 2008.

On July 30, 2008, the House passed H.R. 6432, as amended, under suspension. The engrossed (House-passed) bill incorporated an amended version of H.R. 6432 (ADUFA reauthorization), as reported, and H.R. 6433 (AGDUFA), as reported, without amendment. On August 1, 2008, the Senate took up the House-passed measure and passed it by unanimous consent. The measure has been sent to the President, who is expected to sign it.

This report discusses aspects of ADUFA I, including funding and program performance; FDA’s ADUFA II and AGDUFA proposals; congressional activity; and relevant issues. **Appendix A** provides a summary of ADUFA I. **Appendix B** describes the FDA process for approval of animal drugs. This report will be updated to incorporate legislative actions and other events as they unfold.

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Background

The Animal Drug User Fee Act of 2003 (ADUFA I, P.L. 108-130) was signed by the President in November 2003. It established a new requirement, effective in FY2004, for FDA to collect fees from sponsors of brand-name animal drugs in order to reduce the backlog of reviews for those products, decrease the time required for future reviews, and improve the predictability of the review process. Representatives of animal drug research and development companies say that an animal drug can take 7 to 10 years to develop, at a cost of \$100 million or more.¹ Predictable and timely review is important to these companies. Companies that make generic animal drugs, which are not currently covered by a user fee program, want review of their products to be timely and predictable as well.² Moreover, veterinarians, animal producers, pet owners, and consumers have an interest in the safety, availability, and affordability of animal drugs, including their safety when used in livestock production.

Animal drug user fee authority sunsets October 1, 2008.³ If the program were not reauthorized by then, FDA would have been prohibited at that time from collecting user fees, and would have to lay off animal drug review staff. FDA began discussions with animal drug sponsors regarding ADUFA reauthorization (ADUFA II) in the spring of 2007. In 2008, FDA published its reauthorization proposal in the *Federal Register* in February, held a public meeting in March, and accepted public comments through mid-April. On April 24, 2008, FDA published draft legislation to reauthorize ADUFA, along with a proposal for a new user fee authority for generic animal drug reviews. On July 8, 2008, bills were introduced in the House to reauthorize ADUFA (H.R. 6432) and to establish a user fee program for generic animal drugs (H.R. 6433). Both bills were forwarded without amendment to the full committee by the House Energy and Commerce Subcommittee on Health the following day, and were marked up by the full committee on July 16, 2008. On July 30, 2008, the House passed H.R. 6432, as amended, under suspension. The engrossed bill incorporated an amended version of H.R. 6432, as it was reported by the full committee, and H.R. 6433, the proposal for generic animal drugs, as it was reported. On August 1, 2008, the Senate took up the House-passed measure and passed it by unanimous consent. The measure has been sent to the President, who is expected to sign it.

Reauthorization of the existing user fee program was supported by animal drug research and development companies, livestock producers, and the American Veterinary Medical Association. Because a sunset of program authority would have been highly disruptive to the animal drug review process, many supporters felt that ADUFA reauthorization was “must pass” legislation in the 110th Congress. A coalition of consumer groups opposed the user fee program and its reauthorization, however, citing concerns about the safety of animal drugs approved for livestock production.

This report discusses aspects of ADUFA I, including funding and program performance; FDA’s proposed changes for ADUFA II; FDA’s proposal for a new generic animal drug user fee program; congressional activity; and relevant issues. **Appendix A** provides a summary of ADUFA I. **Appendix B** describes the FDA process for approval of animal drugs. This report will

¹ See comments of Dr. Richard Carnavale, Vice President for Scientific and Regulatory Affairs, Animal Health Institute, at FDA public meeting on ADUFA reauthorization, March 11, 2008, at <http://www.fda.gov/cvm/ADUFA032008Transcript.htm>. Many of these companies are members of the Animal Health Institute, the trade association that represents their interests, at <http://www.ahi.org/>.

² Many of these companies have formed the Generic Animal Drug Alliance, at <http://www.fda.gov/cvm/ADUFAIIPresBatliner.htm>.

³ The law says that ADUFA user fee authority “shall not be in effect *after* October 1, 2008” (emphasis added). [21 U.S.C. § 379j-11 note].

be updated to incorporate legislative actions and other events as they unfold. References in this report to “the Secretary” refer to the Secretary of Health and Human Services (HHS).

Overview of ADUFA I

Legislative History

The Animal Drug User Fee Act of 2003 (ADUFA I, P.L. 108-130) established, for the first time, effective in FY2004, authority for FDA to collect fees from sponsors of animal drugs in order to reduce the backlog of application reviews for those products, and to decrease the time required for future reviews. The act mirrored many provisions from the existing prescription drug and medical device user fee programs.⁴ ADUFA authority is in sections 739-740 of the FDCA [21 U.S.C. §§ 379j-11 and -12]. With the exception of one technical and one conforming amendment in 2007, the law has not been amended since its original passage.⁵ ADUFA I authority sunsets October 1, 2008, the beginning of the FY2009 fiscal year. A summary of the law is provided in **Appendix A**.

The bills that were ultimately enacted in the 108th Congress were H.R. 1260 and S. 313. In its report on the House bill, the House Committee on Energy and Commerce noted that in 1992, FDA was required to report to Congress regarding the feasibility of a user fee program to improve the review process for animal drugs.⁶ In 1994, FDA reported that inadequate review resources, a growing workload, and low-quality applications submitted by industry had slowed the approval process to an unacceptable rate. The FDA report noted that if Congress were to consider legislation authorizing FDA to impose and collect user fees, approximately \$11 million in fees would be needed annually. The committee reported that as of 2003, the situation had not improved, and may have worsened.

In its report on the Senate bill, the Senate Committee on Health, Education, Labor, and Pensions said that animal drug user fee authority should allow FDA to (1) eliminate existing backlogs of applications within two years; (2) over a five-year period, move toward the goal of completing the review of 90% of new animal drug applications within 180 days; (3) resolve new and emerging scientific issues that affect the ability of FDA to make approval decisions; and (4) achieve an enhanced and predictable review performance.⁷

Covered Products

ADUFA I authorizes the collection of user fees for the review of pioneer animal drugs, the so-called “(b)(1)” animal drugs. It does not authorize the collection of fees for ANADAs, the so-called “(b)(2)” generic animal drugs.⁸ The law requires the Secretary, to the extent practicable, to

⁴ See CRS Report RL33914, *The Prescription Drug User Fee Act (PDUFA): History, Reauthorization in 2007, and Effect on FDA*, by Susan Thaul, and CRS Report RL34571, *Medical Device User Fees and User Fee Acts*, by Erin D. Williams.

⁵ P.L. 110-85, The Food and Drug Administration Amendments Act of 2007, § 109, 121 Stat. 842, September 27, 2007.

⁶ H.Rept. 108-287, to accompany H.R. 1260, the Animal Drug User Fee Act of 2003, referring to P.L. 102-571, the Prescription Drug User Fee Act of 1992, § 108(a).

⁷ S.Rept. 108-51, to accompany S. 313, the Animal Drug User Fee Act of 2003.

⁸ If safety or effectiveness data are required for a request to change an approved generic animal drug application (such as approval for a new species) it is considered a supplemental animal drug application, and is subject to a user fee under ADUFA.

segregate the review of ANADAs from that of NADAs, and adopt other administrative procedures to ensure that review times of ANADAs do not increase because of activities under the user fee program.

Covered Activities

ADUFA I defines the activities and costs that are allowable under the user fee program, including those related to personnel, management of information and facilities, and fee collection, for the review of applications.⁹ The definitions do not include any postmarket activities, and expressly prohibit the use of user fees to review advertising and labeling after an animal drug has been approved.

Fee “Triggers”: Authority to Collect Fees

Congress established, in ADUFA I, three funding “triggers” that prohibit FDA from collecting user fees for animal drug review unless certain conditions are met each year. This was done to ensure that user fees supplement, rather than replace, appropriated funds. Two of the triggers set FY2003 as a baseline, a minimum level of non-user fee appropriations (adjusted for inflation) that must be maintained each year. One of these triggers requires that this level be maintained across the agency. The other requires that it be maintained specifically for animal drug review activities. The third trigger prohibits FDA from collecting user fees unless an explicit amount for such fees is authorized in annual appropriations. The triggers are as follows:

- FDA’s overall appropriation for salaries and expenses for a given fiscal year, excluding fees, must exceed the agency’s overall appropriation for salaries and expenses for FY2003 (prior to the user fee program), excluding fees, and adjusted for inflation.¹⁰
- FDA must spend, for animal drug review, from appropriated funds, an amount not more than 3% below the amount spent for animal drug review, from appropriated funds, in FY2003 (prior to the user fee program), under certain conditions. Under no condition may such amount be more than 5% below the FY2003 amount. (Amounts in either case are adjusted for inflation).¹¹
- Fees shall be collected and available for obligation only to the extent and in the amount provided in advance in annual appropriations acts.¹²

In its annual financial reports to Congress for fiscal years 2004 through 2006 (the most recent available), as required by ADUFA I, FDA reports that each of the fee triggers was met each year.¹³

Types of Fees

Experience from the human drug and medical device user fee programs showed that because the number of applications varies from year to year, basing a user fee program solely on application fees did not provide predictable funding streams. From the outset, ADUFA I authorized several

⁹ FFDCA §§ 739(8) and (9) [21 U.S.C. §§ 379j-11(8) and (9)].

¹⁰ FFDCA § 740(f)(1), [21 U.S.C. § 379j-12(f)(1)].

¹¹ FFDCA § 740(g)(2), [21 U.S.C. § 379j-12(g)(2)].

¹² FFDCA § 740(g)(1), [21 U.S.C. § 379j-12(g)(1)].

¹³ ADUFA reports are available at <http://www.fda.gov/cvm/adufa.htm>.

types of user fees. The act also authorized the total revenues for each fee type that may be collected each fiscal year, which are to be adjusted annually for inflation and workload. The act required the Secretary to set annual fees at least 60 days before the start of each fiscal year and to publish the fees and methodology in the *Federal Register*. The types of animal drug user fees, and the fee amounts for FY2008, are as follows:

- *Application fees:* One-time fees for new animal drug applications (NADAs), and NADA supplements for which safety or effectiveness data are required.¹⁴ Supplement fees are half the amount of the NADA fee. The FY2008 amounts are \$172,500 per NADA and \$86,250 for a NADA supplement for which safety or effectiveness data are required.
- *Product fees:* Annual fees for each of a sponsor's products to which ADUFA is applicable, including approved and pending applications. The FY2008 amount is \$4,125.
- *Establishment fees:* Annual fees for each of a sponsor's manufacturing establishments, unless the product is not manufactured in the year the fee would be assessed. The FY2008 amount is \$52,700.
- *Sponsor fees:* Annual fees for each sponsor of an approved or pending application. The FY2008 amount is \$43,900.¹⁵

Sponsor fees apply only if the sponsor has had, since September 1, 2003, a pending NADA, NADA supplement or investigational new animal drug (INAD) submission. Product and establishment fees apply only if the sponsor has had, since September 1, 2003, a pending NADA or NADA supplement. ADUFA I establishes that total revenues for each type of fee should comprise one-fourth of total fee revenues, but the actual proportion of each type of fee collected each year typically varies slightly from these projections. FDA publishes information about fee collections in its annual financial reports to Congress, as required by ADUFA I.

Fee Waivers

ADUFA I authorizes the Secretary to waive or reduce fees if he determines that one or more of the following applies:

- Assessing the fee would be a barrier to innovation.
- Fees would exceed FDA's present and anticipated future costs for conducting reviews.
- The application is intended solely for a minor reformulation of an approved drug for use in animal feed.
- The application is intended solely to provide for a minor use or minor species indication.
- The sponsor is a small business submitting its first animal drug application. The law defines a small business as one having fewer than 500 employees, including employees of affiliates.

¹⁴ See **Appendix B** for a description of the FDA approval process for animal drugs.

¹⁵ ADUFA fee information is available at <http://www.fda.gov/cvm/adufa.htm>.

Information about the numbers and value of waivers and reductions granted and used is provided in FDA's annual financial reports. The most common waivers granted were fees for sponsors of approved or pending applications for minor use or minor species indications.

Program Performance

Brand-Name Animal Drugs

ADUFA I performance goals were developed following consultation between FDA and the regulated industry, primarily to address the backlog of animal drug reviews and to shorten review times in the future. The goals were not incorporated in the statute, which instead refers to the goals as identified in the Secretary's letter to the chairmen and ranking members of the House Committee on Energy and Commerce, and the Senate Committee on Health, Education, Labor, and Pensions.¹⁶ Animal drug submissions to FDA vary considerably in their complexity. By agreement between FDA and the industry, a subset of six submission types were chosen as being the most meaningful for performance measurement, and are referred to as *sentinel submissions*. **Table 1** displays the performance goals that apply to the five-year ADUFA I performance period of FY2004 through FY2008. FDA was to review and act on 90% of sentinel submissions within the specified amounts of time. The goals were to be phased in to achieve progressive improvements in the timeliness of review.

Table 1. ADUFA I Performance Goals

| Activity | FDA Review Time (days) | | | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|--------|--------|--------|--------|
| | FY2004 | FY2005 | FY2006 | FY2007 | FY2008 |
| The goal is to review and act on 90% of submissions within the stated time. | | | | | |
| Non-administrative NADAs and reactivations | 295 | 270 | 230 | 200 | 180 |
| Non-manufacturing supplemental NADAs and reactivations ^a | 320 | 285 | 235 | 200 | 180 |
| Manufacturing supplemental NADAs and reactivations ^b | 225 | 190 | 140 | 120 | 120 |
| INAD submissions of study data | 320 | 285 | 235 | 200 | 180 |
| INAD submissions of study protocols | 125 | 100 | 80 | 60 | 50 |
| Administrative NADAs | 90 | 85 | 80 | 70 | 60 |
| Interim backlog goals | | | | | |
| Review and act on pending applications, supplemental applications, and INAD submissions within 24 months of initiation of user fee payments. | | | | | |
| Additional interim goals | | | | | |
| Fifty percent of FDA incremental review staff recruited and on board by first quarter of FY2006. Total staff increment on board by end of FY2008. | | | | | |
| FDA will review all submissions in accordance with procedures for working within a queue. An application/submission that is not reviewed within the applicable time frame will be reviewed with the highest possible priority among those pending. | | | | | |

¹⁶ This letter, dated November 13, 2003, is published as an appendix in FDA's annual ADUFA performance reports, at <http://www.fda.gov/cvm/adufa.htm>.

- a. Non-manufacturing supplemental applications are those that require safety and effectiveness data.
- b. Manufacturing supplemental applications are typically less complicated, requiring data on manufacturing, processing, packaging and related activities.

According to the required annual performance reports for FY2004 through FY2006 (the most recent available), FDA says that all timeliness goals were met or exceeded during each year of program performance. Also, the agency reports that, as proposed, the submission backlog was eliminated by the end of FY2004, the goal of having 50% of additional review staff recruited and on-board by the first quarter of FY2006 was met, improvements were made in staff training and business systems, and several guidance documents were published.

Generic Animal Drugs

Section 512(c)(1) of the FFDCA requires FDA to review and act on abbreviated new animal drug applications (ANADAs, which are generic animal drug applications) within 180 days of submission.¹⁷ In congressional testimony in June 2008, FDA reported that in FY2007, the average review time for ANADAs was 570 days, and there was a backlog of 446 of these submissions, almost double the number in FY2000.¹⁸ The review of ANADAs is funded entirely through appropriations. ADUFA user fee funds may not be applied to generic animal drug reviews.

The Secretary's letter to congressional committees regarding ADUFA performance goals did not address goals for the review of ANADAs. ADUFA I requires that the Secretary, to the extent practicable, segregate the review of ANADAs from the process for user fee-funded reviews and adopt other administrative procedures to ensure that review times for ANADAs do not increase as a result of activities under the user fee program. The act also requires that FDA include, in its annual performance reports to Congress, information about review times for ANADAs, and about the required administrative procedures. The annual performance reports do not provide quantitative information regarding ANADA submissions and review times. They note that FDA maintains separate staffing and queues for ANADAs, and has defined baseline performance levels from FY2001 through FY2003, against which to measure current performance. In its annual performance reports, FDA says that ANADA review times did not increase in FY2004, but did increase in FY2005 and FY2006, which the agency attributes to understaffing.

Table 2 compiles CVM workload data for the animal drug program overall (i.e., for both brand-name and generic drugs) for FY2004 through FY2009, noting the numbers of submissions received, completed, approved, and pending. It is not valid to directly compare program outputs for ADUFA activities in **Table 2** against the goals in **Table 1**. **Table 2** does not present information about review times, and it is not possible to know which submissions in **Table 2** represent the sentinel submissions to which the performance goals are applied. Also, submissions acted upon (or not) in a given year are not necessarily subsets of the number of submissions received that year. Nonetheless, **Table 2** (shaded rows) shows a steady increase in the number of pending ANADA supplements and a decline in the number of them completed each year, neither of which appears to be explained by the annual number of applications.

¹⁷ The FDA must, within that time, either issue an order approving the application, or offer the sponsor a notice of opportunity for hearing regarding the agency's finding, pursuant to FFDCA §512(d)(1), of a basis for withholding approval. See **Appendix B** for a description of the FDA approval process for animal drugs.

¹⁸ Testimony of Bernadette M. Dunham, Director, FDA CVM, before the House Committee on Energy and Commerce, Subcommittee on Health, hearing on "Committee Prints on Administration Legislative Proposals on the Animal Drug User Fee Act Amendments of 2008 and the Animal Generic Drug User Fee Act of 2008," June 5, 2008, 110th Cong., 2nd Sess., Washington, DC.

Table 2. Animal Drug Program Activities

| Submission type | FY2004 actual | FY2005 actual | FY2006 actual | FY2007 actual | FY2008 estimate | FY2009 estimate |
|------------------------------------------------------------------------------|----------------------|----------------------|----------------------|----------------------|------------------------|------------------------|
| Applications and activities covered by ADUFA I user fee authority | | | | | | |
| NADAs | | | | | | |
| Received | 15 | 11 | 16 | 21 | 20 | 20 |
| Completed | 23 | 9 | 13 | 22 | 22 | 23 |
| Approved | 18 | 7 | 6 | 18 | 19 | 19 |
| Pending | 3 | 5 | 8 | 7 | 5 | 2 |
| NADA supplements | | | | | | |
| Received | 408 | 451 | 598 | 605 | 605 | 605 |
| Completed | 476 | 449 | 561 | 610 | 618 | 627 |
| Approved | 356 | 319 | 430 | 496 | 540 | 540 |
| Pending | 156 | 159 | 195 | 187 | 174 | 152 |
| Investigational new animal drug (INAD) files | | | | | | |
| Received | 2,138 | 1,888 | 2,193 | 2,457 | 2,457 | 2,464 |
| Completed | 2,200 | 1,767 | 2,231 | 2,491 | 2,491 | 2,491 |
| Pending | 264 | 386 | 351 | 320 | 286 | 259 |
| Applications and activities not covered by ADUFA I user fee authority | | | | | | |
| ANADAs | | | | | | |
| Received | 61 | 49 | 45 | 23 | 24 | 27 |
| Completed | 55 | 46 | 43 | 37 | 35 | 32 |
| Approved | 19 | 13 | 17 | 20 | 18 | 18 |
| Pending | 47 | 50 | 52 | 38 | 27 | 22 |
| ANADA supplements | | | | | | |
| Received | 211 | 116 | 127 | 142 | 143 | 149 |
| Completed | 195 | 97 | 120 | 88 | 86 | 82 |
| Approved | 163 | 71 | 80 | 71 | 69 | 69 |
| Pending | 78 | 99 | 104 | 157 | 214 | 281 |
| Generic investigational new animal drug (JINAD) files | | | | | | |
| Received | 170 | 335 | 191 | 145 | 160 | 160 |
| Completed | 130 | 229 | 321 | 149 | 140 | 140 |
| Pending | 66 | 173 | 42 | 38 | 58 | 78 |

Source: Annual FDA Congressional Budget Justifications, FY2006 through FY2009, Animal Drugs and Feeds sections, Animal Drugs and Feeds Program Activity Data (PAD) tables.

Program Funding and Financial Reports

ADUFA I authorized the following funding levels for its five-year program period, from FY2004 through FY2008, as follows:

- \$5 million for FY2004,
- \$8 million for FY2005, and
- \$10 million for each of fiscal years 2006 through 2008.

Each amount is subject to the inflationary and workload adjustments required by ADUFA I. The Secretary also has authority, but is not required, to apply a final-year adjustment to the FY2008 amount, to provide up to three months of carryover into FY2009. An adjustment for the full three months was included in the agency's FY2008 budget request and was provided in the amount authorized in FY2008 appropriations.

ADUFA I requires the Secretary to submit to Congress, within 120 days of the end of each fiscal year, annual financial reports about the user fee program. FDA has published reports for fiscal years 2004 through 2006.¹⁹ The reports address the three funding triggers, each of which has been met each fiscal year. They also present total costs for the process of review of animal drug applications, as defined in ADUFA I, and the amounts paid from user fee revenues and appropriations. These costs are principally borne by FDA CVM, but also, to a lesser extent, by the Office of the Commissioner (OC) and the Office of Regulatory Affairs (ORA). OC supports general and administrative functions. ORA supports pre-approval inspections of manufacturing facilities, investigations of clinical studies, and analytical testing of samples that are counted for the review process for animal drug applications.

Table 3 presents the funding history for the ADUFA I program period of FY2004 through FY2008, with FY2003 provided as a baseline. (FY2003 appropriations levels for animal drug review serve as the baseline for one of the three funding triggers.) User fee funds have grown as a proportion of total funding for animal drug review, accounting for almost one-fourth of total funding in FY2006.²⁰ Obligations from direct appropriations grew by about 12% overall between FY2003 and FY2006. User fee revenues available during the ADUFA I program period totaled almost \$50 million, including the final year adjustment in FY2008 for carryover into FY2009.

Table 3. ADUFA I Funding History, FY2003-FY2008

(dollars in thousands)

| Fiscal Year | Obligations from Direct Appropriations ^a | User Fees ^b | Total | User Fees/ Total (%) |
|-----------------------|-----------------------------------------------------|------------------------|-----------|----------------------|
| FY2003 | \$32,748 | NA | \$32,748 | 0 |
| FY2004 | 31,774 ^c | 5,000 | 36,774 | 13.6 |
| FY2005 | 34,408 | 8,354 | 42,762 | 19.5 |
| FY2006 | 36,637 | 11,318 | 47,955 | 23.6 |
| FY2007 | not published | 11,604 | NA | NA |
| FY2008 | not published | 13,696 ^d | NA | NA |
| Total: ADUFA I | NA | \$49,972 | NA | NA |

Notes: NA is not applicable. User fees were first authorized for FY2004. FDA has published amounts obligated to the animal drug review program from direct appropriations only for fiscal years 2003 through 2006. Annual

¹⁹ See <http://www.fda.gov/cvm/adufa.htm>.

²⁰ User fees made up a larger proportion of total funds available for human drug reviews during the same period. See Table 2B in CRS Report RL33914, *The Prescription Drug User Fee Act (PDUFA): History, Reauthorization in 2007, and Effect on FDA*, by Susan Thaul. User fees made up a smaller proportion of total funds for medical device reviews. See Table 4 in CRS Report RL33981, *Medical Device User Fee and Modernization Act (MDUFMA) Reauthorization*, by Erin D. Williams.

percentages and totals can be calculated only for those years for which there are published amounts for these obligations.

ADUFA I does not have explicit requirements regarding full-time equivalent (FTE) staffing positions for animal drug review, and FDA has not published information about these positions that is comparable from one fiscal year to the next.

- a. From FDA Annual ADUFA Financial Reports for FY2004 through FY2006, at <http://www.fda.gov/cvm/adufa.htm#Reports>. Includes only direct appropriations, not user fee amounts specified in annual appropriations acts.
- b. Amounts as specified in annual appropriations acts.
- c. Though this amount is less than the FY2003 baseline, this trigger in ADUFA I provides that FDA may collect user fees as long as the amount obligated for animal drug reviews is not more than 3% below the FY2003 baseline, adjusted for inflation. Because of the 3% cushion, this requirement was met in FY2004.
- d. Amount reflects, in addition to inflationary and workload adjustments, the final year adjustment, pursuant to ADUFA I at FFDCA § 740(c)(3) [21 U.S.C. § 379j-12(c)(3)], for carryover into the first three months of FY2009.

Sunset Provision

ADUFA I user fee authority sunsets October 1, 2008. FDA would have been prohibited from collecting user fees after this date, unless the program were reauthorized.²¹ If not, absent other sources of funds, the agency would have to lay off animal drug review staff.²² Personnel regulations require that federal agencies give staff 60 days notice of an impending reduction in force (RIF).²³ In 2007, as similar authorities for human drugs and devices were about to sunset, the FDA Commissioner expressed concern to Congress about the potential attrition of staff who feared losing their jobs, and the desire to avoid having to send the required RIF notice.²⁴

FDA Proposal for ADUFA Reauthorization

Timeline

ADUFA I directs FDA to (1) develop a reauthorization proposal for fiscal years 2009 through 2013 (ADUFA II), in consultation with Congress and stakeholders; (2) publish its proposed recommendations in the *Federal Register*; (3) hold a public meeting thereafter; (4) provide a 30-day public comment period; and, finally, (5) present its final recommendations to the Congress. On February 21, 2008, FDA published its proposal for ADUFA II, which was developed based on a public meeting in April 2007 and discussions with the regulated industry.²⁵ FDA held another public meeting to present its proposal and receive comments on March 11, 2008. Written

²¹ ADUFA's requirements for reports to Congress sunset 120 days later, which maintains the annual performance and financial reporting requirement for FY2008, whether or not the program were reauthorized.

²² FDA estimated that 58 employees would have been affected by such layoffs. See Testimony of Bernadette M. Dunham, Director, FDA CVM, before the House Committee on Energy and Commerce, Subcommittee on Health, hearing on "Committee Prints on Administration Legislative Proposals on the Animal Drug User Fee Act Amendments of 2008 and the Animal Generic Drug User Fee Act of 2008," June 5, 2008, 110th Cong., 2nd Sess., Washington, DC.

²³ See U.S. Office of Personnel Management, "Summary of Reduction in Force Under OPM's Regulations," at <http://www.opm.gov/rif/general/rifguide.asp>.

²⁴ See "FDA Chief Again Presses Congress On User Fees, Says 1997 Delay Caused Severe Setbacks," *InsideHealthPolicy.com*, September 17, 2007.

²⁵ 73 *Federal Register* 9571-9575, February 21, 2008.

comments were due to the agency on April 14, 2008. FDA's legislative proposal to the Congress was published on April 24, 2008.²⁶

Content

According to the *Federal Register* notice, FDA's proposed reauthorization would maintain most of the basic architecture of ADUFA I. The draft ADUFA II legislation, published on April 24, 2008, largely reflects the *Federal Register* proposal. Significant proposed changes to program financing and performance goals are discussed in greater depth below.²⁷ The agency's proposal does not address matters related to postmarket activities. A separate proposal to establish a user fee program for the review of generic animal drugs is discussed in a subsequent section of this CRS report.

Program Financing

FDA says that user fees have not kept up with the increase in program costs that result from what the agency calculates as 5.9% annual inflationary growth in pay and benefits, and rent and rent-related costs, over the ADUFA I program period. The agency proposes higher levels of fee revenues for the ADUFA II program period, above those that would result solely from the inflation adjustments in current authority. **Table 4** presents FDA's proposed authorization levels for ADUFA II fee revenues, based on the agency's projections. The recommended levels total \$98 million over five years, almost twice the funding level of the five-year ADUFA I program period (see **Table 3**). FDA proposes to eliminate the current inflation adjustment provisions for fee revenues (because such adjustments are incorporated in the proposed revenue targets), and suggests a number of additional technical changes to fee authority. The agency proposes to leave the current fee triggers unchanged throughout the ADUFA II program period.

**Table 4. FDA Proposed ADUFA II Funding Levels,
FY2009-FY2013**

(dollars in thousands)

| Fiscal Year | FY2009 | FY2010 | FY2011 | FY2012 | FY2013 | Total |
|---------------------------------|--------|--------|--------|--------|--------|----------|
| Authorization of appropriations | 15,260 | 17,280 | 19,448 | 21,768 | 24,244 | \$98,000 |

Source: 73 *Federal Register* 9571-9575, February 21, 2008.

Enhancements to Performance Goals²⁸

FDA proposes to retain the same initial time frames for review throughout the ADUFA II program period as those in place in FY2008 (see **Table 1**). Per discussions with industry, the agency proposes to add an "end review amendment" process. It would allow the agency to work with sponsors to make minor amendments to a submission, rather than designating the review as

²⁶ FDA, "Animal Drug User Fees," April 24, 2008, at http://www.fda.gov/oc/opacom/hottopics/adufa_agdufa/adufareauth.html.

²⁷ The reauthorization proposal also includes several technical changes. FDA has listed the differences between ADUFA I and its ADUFA II legislative proposal at http://www.fda.gov/oc/opacom/hottopics/ADUFA_AgDUFA/ADUFAIIsummary.html.

²⁸ FDA has published its proposed performance goals and procedures for ADUFA reauthorization at <http://www.fda.gov/cvm/ADUFAIIreauthorization.htm>.

incomplete, which “re-sets the clock” for an additional review cycle.²⁹ Other proposals agreed to by FDA and the industry include holding public workshops, implementing procedures to streamline scheduling of foreign facility pre-approval inspections, and discussing the applicability of pharmacokinetic and pharmacodynamic data in the review process, among others. In addition, FDA proposes to develop an electronic tool for industry submissions and online review capability within 24 months of an ADUFA appropriation for FY2009.

FDA Proposal for Generic Animal Drug User Fees

Though ADUFA I required FDA to take steps to ensure that the user fee program did not compromise the timeliness of generic animal drug reviews, FDA has had difficulty keeping up with these reviews, and has not generally met the statutory requirement to act on ANADAs within 180 days. (See the earlier section on “Program Performance”.) It is not clear whether this is a result of the user fee program, a result of a failure of non-fee funding to keep pace with demand in the generics program (which may have occurred regardless of the user fee program), or other factors. In its FY2009 budget request, FDA proposed, for the first time, a user fee program to support reviews of generic animal drugs. At an ADUFA public meeting in 2007, a representative of the Generic Animal Drug Alliance (GADA) announced the Alliance’s support for a generic animal drug user fee program.³⁰

On April 24, 2008, FDA published a draft legislative proposal for the Animal Generic Drug User Fee Act (AGDUFA), accompanied by performance goals for generic animal drug review that were agreed to in consultation with the industry.³¹ The agency noted the increasing review times for generic animal drugs, saying that the workload was likely to grow, because patent protection on approximately 49 animal drugs will expire between FY2009 and FY2011. The AGDUFA proposal is similar in design to ADUFA I, including, for example, comparable fee triggers (one of them requiring maintenance of non-user fee funding for generic animal drug reviews), fee-setting requirements, workload adjustments, and reporting requirements. Like FDA’s ADUFA II proposal, the AGDUFA proposal has fixed annual increases instead of the ADUFA I inflation adjuster. Notable differences between ADUFA I and the AGDUFA proposal include the following:

- AGDUFA authority to collect application, product, and sponsor fees, but not establishment fees.
- AGDUFA sponsor fees (for which a given sponsor would pay only one fee per year) that are tiered according to the number of a sponsor’s currently approved ANADAs.
- AGDUFA authority to waive or reduce fees only if the drug is intended for a minor use or minor species indication.

Table 5 presents FDA’s proposed authorization levels for AGDUFA fee revenues for FY2009 through FY2013.

²⁹ The process is described in the transcript of the FDA public meeting on ADUFA reauthorization, March 11, 2008 (hereafter referred to as ADUFA meeting transcript), at <http://www.fda.gov/cvm/ADUFA032008Transcript.htm>.

³⁰ Presentation of Stephanie Batliner, representing the Generic Animal Drug Alliance, ADUFA public meeting, April 27, 2007, at <http://www.fda.gov/cvm/ADUFA07PM.htm>.

³¹ FDA, “Animal Drug User Fees,” April 24, 2008, at http://www.fda.gov/oc/opacom/hottopics/adufa_agdufa/adufareauth.html.

**Table 5. FDA Proposed AGDUFA Funding Levels,
FY2009-FY2013**

(dollars in thousands)

| Fiscal Year | FY2009 | FY2010 | FY2011 | FY2012 | FY2013 | Total |
|---------------------------------|--------|--------|--------|--------|--------|----------|
| Authorization of appropriations | 4,831 | 5,106 | 5,397 | 5,706 | 6,031 | \$27,071 |

Source: FDA, “Animal Drug User Fees,” April 24, 2008, at http://www.fda.gov/oc/opacom/hottopics/adufa_agdufa/adufareauth.html.

FDA’s proposed performance goals for AGDUFA are similar to those for ADUFA I. The agency proposes to review and act on 90% of five “sentinel” types of generic animal drug submissions within specific time frames, which decrease steadily from FY2009 through FY2013. (As noted earlier, FFDCA §512(c)(1) requires the FDA to act on all such submissions within 180 days.) In FY2009, the proposed target to act on certain submissions is as long as 700 days (almost two years). By FY2013, the longest proposed target is 270 days. The agency did not propose any AGDUFA performance goals regarding the backlog of reviews, or other matters.

In congressional testimony in June 2008, a witness representing GADA testified that according to its agreement with FDA regarding an animal generic drug user fee program (as reflected in FDA’s AGDUFA proposal), “the performance goals for AGDUFA do not return generic application review times to [the statutory requirement of 180 days]. Rather, 270 days is the highest level of performance that the generic animal drug industry could afford.”³²

Congressional Action

Hearings

On June 5, 2008, the House Energy and Commerce Subcommittee on Health held a hearing on ADUFA reauthorization and the Administration’s ADUFA II and AGDUFA proposals.³³

Subcommittee Members in attendance expressed a number of points of view regarding the forthcoming legislative process. While all of them expressed general support for both proposals, some stated a preference for efficient passage of a “clean” ADUFA reauthorization, while others suggested that one or the other proposal could serve as a vehicle for additional subject matter that was not part of the FDA-industry agreements. Such subject matter included postmarket safety—in particular, public health concerns about antimicrobial resistance—and certain expansions of FDA’s enforcement authority that are currently under consideration in the House and Senate. These matters are discussed in greater detail in the next section of this CRS report, “Issues for Congress”.

³² Testimony of Stephanie Batliner, representing GADA, before the House Committee on Energy and Commerce, Subcommittee on Health, hearing on “Committee Prints on Administration Legislative Proposals on the Animal Drug User Fee Act Amendments of 2008 and the Animal Generic Drug User Fee Act of 2008,” June 5, 2008, 110th Cong., 2nd Sess., Washington, DC, hereinafter referred to as House Subcommittee hearing.

³³ House Subcommittee hearing.

Legislation

Overview

On July 8, 2008, bills were introduced in the House to reauthorize ADUFA (**H.R. 6432**) and to establish a user fee program for generic animal drugs (**H.R. 6433**). Both bills were forwarded without amendment to the full committee by the House Energy and Commerce Subcommittee on Health on July 9, and marked up and passed by the full committee on July 16. On July 30, 2008, the House passed H.R. 6432, as amended, under suspension. The engrossed bill incorporated an amended version of H.R. 6432 (ADUFA reauthorization) as reported, and H.R. 6433 (AGDUFA), as reported. On August 1, 2008, the Senate took up the House-passed measure, and passed it by unanimous consent. The measure has been sent to the President, who is expected to sign it.

House Action

H.R. 6432, the Animal Drug User Fee Amendments of 2008, as introduced, would reauthorize ADUFA, largely in line with FDA's proposal. Rather than the inflation adjuster in current law, the bill would authorize a total of \$98 million for the program over the five-year period from FY2009 through FY2013, as requested by FDA and depicted in **Table 4**. The bill would extend, among other provisions, (1) existing authority for the collection of application, product, establishment, and sponsor fees (with authority to collect larger aggregate amounts of each type of fee in each successive fiscal year); (2) the fee triggers; and (3) requirements for annual fiscal and performance reports. Program authority would sunset on October 1, 2013, and reporting requirements would sunset four months later, on January 31, 2014. The bill would not explicitly establish performance goals. Rather, it refers in a finding to goals as laid out in a letter from the Secretary to the Congress. Upon the bill's passage, such a letter would presumably be included in the Congressional Record as stated in the finding, and comport with the goals as published by FDA in its reauthorization proposal,³⁴ unless the goals were modified during passage.

H.R. 6432, as introduced, contains two provisions that were in neither ADUFA I nor the FDA reauthorization proposal. The first are new requirements for public involvement in the reauthorization planning that would begin prior to the FY2013 sunset. Provisions in Section 4 of the bill would require the Secretary to (1) seek public input *before* beginning negotiations with industry to reauthorize the program; (2) hold periodic consultations with other stakeholder groups (e.g., consumer representatives) during such negotiations; and (3) publish transcripts of all negotiation meetings between the FDA and the regulated industry. These requirements would be in addition to the current requirement to seek public input at the conclusion of negotiations with industry. The second new provision, in Section 5 of the bill, would alter the reporting period for required drug experience reports (i.e., reports that companies must make to FDA if they are aware of a product problem or defect), as currently required by regulation. The bill, as introduced, would not authorize FDA to use program fees for postmarket activities, and would not establish any new data reporting requirements for industry.

H.R. 6433, the Animal Generic Drug User Fee Act of 2008, as introduced, would establish a new animal generic drug user fee program, largely in line with FDA's proposal. The bill would establish authority to collect application, product, and tiered sponsor fees (but not establishment fees), and would establish fee triggers, fee-setting requirements, workload adjustments, and reporting requirements. Rather than using an inflation adjuster, the bill would authorize a total of

³⁴ FDA has published its proposed performance goals and procedures for ADUFA reauthorization at <http://www.fda.gov/cvm/ADUFAIReauthorization.htm>.

about \$27 million for the program over the five-year period from FY2009 through FY2013, as requested by FDA and depicted in **Table 5**. Program authority would sunset on October 1, 2013, and reporting requirements would sunset four months later, on January 31, 2014. As with H.R. 6432, the generics bill would not explicitly establish performance goals, but refers to such goals in a finding.³⁵ Also as with H.R. 6432, the bill would require the Secretary to seek public input before beginning negotiations with industry to reauthorize the program, hold periodic consultations with other stakeholder groups during such negotiations, and publish transcripts of all negotiation meetings between the FDA and the regulated industry, in addition to a requirement to seek public input at the conclusion of negotiations with industry. Finally, as with H.R. 6432, the bill, as introduced, would not authorize FDA to use program fees for postmarket activities, and would not establish any new data reporting requirements for industry.

Both H.R. 6432 and H.R. 6433 were marked up and passed by the full House Energy and Commerce Committee on July 16, 2008. The committee amended H.R. 6432 (ADUFA reauthorization) to make several technical and minor changes, and two substantive changes. First, animal drug sponsors would be required to provide annual reports to FDA regarding any of their animal drugs that contain an antimicrobial active ingredient. Such reports must include specified information about drug distribution, proposed usage, and other matters, and the Secretary would be required to publish such information in a manner that is consistent with national security and business confidentiality concerns. Second, the Secretary would be required to refuse admission to any imported animal drug that appears to be counterfeit, and to destroy any such items, under certain conditions.³⁶ H.R. 6433 was amended to make several technical and minor changes, but no substantive changes.

On July 30, 2008, the House passed an amended version of H.R. 6432 under suspension of the rules. The engrossed (House-passed) version of H.R. 6432 incorporated, as Title I, an amended version of the H.R. 6432 ADUFA reauthorization bill that was reported by the full Energy and Commerce Committee, and, as Title II, all provisions of H.R. 6433 (AGDUFA) as reported, without any substantive changes. The provisions in House-passed Title I of the bill had been amended to remove the earlier amendment made by the full committee regarding refusal of admission and destruction of animal drugs that appear to be counterfeit. The earlier amendment regarding reporting of information regarding animal antimicrobial drugs was retained. The House-passed bill also contained, as Title III, two technical corrections to the Food and Drug Administration Amendments Act of 2007 (FDAAA, P.L. 110-85) that do not apply to animal drugs.

Senate Action

On August 1, 2008, the Senate took up the engrossed (House-passed) version of H.R. 6432 (including reauthorization of ADUFA, the user fee program for generic animal drugs, and the FDAAA technical corrections) and passed it by unanimous consent. The measure has been sent to the President, who is expected to sign it.

Issues for Congress

This section discusses issues germane to congressional consideration of ADUFA reauthorization and the establishment of a user fee program for generic animal drugs. Actual consideration of

³⁵ FDA has published its proposed performance goals and procedures for AGDUFA at http://www.fda.gov/oc/opacom/hottopics/ADUFA_AgDUFA/AgDUFAperfgoals.html.

³⁶ This provision would amend FFDCA § 801(a) [21 U.S.C. § 381(a)] regarding imports.

these issues in moving legislation is tracked in the previous section of this CRS report, “Congressional Action”.

ADUFA Program Performance³⁷

Generally, companies that research and develop animal drugs have been satisfied that ADUFA I has eliminated the review backlog for brand-name animal drugs, improved the timeliness and predictability of reviews, and improved communication with FDA throughout the process. The industry’s focus for ADUFA II was to continue the enhancement of FDA review capacity, including more support for increasingly complex reviews. Also, at the public meeting in March 2008, both FDA and industry speakers discussed a growing backlog of premarket inspections of foreign animal drug producing facilities, which has not been remedied by the current user fee program.

ADUFA Program Costs

The centerpiece of FDA’s reauthorization proposal, as negotiated with industry, was an increase in user fee revenues to reflect cost growth in excess of authorized inflationary adjustments.³⁸ The proposal would authorize FDA to collect almost twice as much in animal drug user fees during the five-year ADUFA II program period (FY2009 through FY2013) as it could during ADUFA I (FY2004 through FY2008). Much of the growth in program costs that FDA cited is driven by factors outside of the agency’s control, such as growth in the costs of employee salaries and benefits, and rents.³⁹

Although a backlog of premarket foreign facility inspections was discussed at the March 2008 public meeting, the FDA proposal did not explicitly address the cost of these inspections. Given recent concerns about the safety of imported drugs and foods, FDA has been under pressure to expand its oversight of foreign facilities that manufacture products it regulates. FDA has not, however, signaled any particular safety concern about foreign plants that manufacture animal drugs, or any changes to the *premarket* inspections of these plants that are conducted for purpose of application review. At present, establishment fees may be assessed for these plants, when applicable, but the fees are not directly linked to inspection costs, and do not distinguish between domestic and foreign facilities.

Animal Drug Safety and Postmarket Review

The aim of drug user fees programs is to speed the evaluation of drugs for safety and effectiveness, without shortchanging the rigor of the evaluation or compromising the actual safety and effectiveness of approved drugs. Critics have charged that the user fee program for human drugs (PDUFA) places too much influence in the hands of industry, and speeds drugs to market with inadequate safety review. They note that the industry is actively involved in establishing performance benchmarks, for example. Also, some feel that consumer confidence in FDA’s

³⁷ See public comments of Dr. Steven D. Vaughn, Director of FDA/CVM/ONADE, and Dr. Richard Carnavale, Vice President for Scientific and Regulatory Affairs, Animal Health Institute, ADUFA meeting transcript.

³⁸ See public comments of Gary Claywell, Deputy Director, FDA/CVM Office of Management, ADUFA meeting transcript.

³⁹ Claywell notes that pay and benefit costs grew by 5.9% annually over the ADUFA I program period, while appropriations grew by 2.6%.

review process is important, and that a perception of conflicts in the user fee programs may undermine this confidence.⁴⁰

It has been difficult to measure the effect of PDUFA, if any, on the safety of human drugs, and unequivocal evidence of such an effect is lacking. The law has, since its second reauthorization, allowed FDA to carry out certain postmarket safety activities with user fee funds. ADUFA I does not have a comparable authority. No postmarket activities are listed in the definition of activities for which fees may be used.⁴¹ For animal drugs, postmarket safety concerns arise on occasion, resulting in withdrawals or label warnings, but noteworthy recent examples preceded ADUFA. FDA's proposal for ADUFA II, as negotiated with industry, did not seek authority to use animal drug user fees for any postmarket activities. It is reported that during ADUFA reauthorization negotiations, FDA sought to have authority to spend user fees on some postmarket antimicrobial resistance activities (discussed further below), but drug companies objected.⁴²

Antimicrobial Resistance

Concerns about the effects of ADUFA on animal drug safety often play out in a different context than that for the safety of human drugs. Some critics of the law are concerned about the safety of drugs approved for animal agriculture with respect to public health and the environment, rather than safety for the treated animal. In particular, they are concerned about antimicrobials (e.g., antibiotics) used in food-producing animals, and the risk of transmitting antimicrobial resistant infections to people through food.⁴³ In general, animal drug companies and livestock producers are concerned that overly stringent regulation of this class of animal drugs could compromise their availability and have harmful effects on animal health without an attendant public health benefit.

FDA has asserted that there is a preponderance of evidence that the use of antimicrobials in food-producing animals has adverse public health consequences, and that there is little evidence to the contrary.⁴⁴ In 2003, FDA published guidance for industry, laying out the agency's information requirements and processes for evaluating animal antimicrobial drugs that may pose this risk.⁴⁵ Review of this class of animal drugs may be more complex than is typical. FDA has not, however, published information about submissions, review times, outcomes, costs, or other metrics specific to this class.

⁴⁰ See CRS Report RL33914, *The Prescription Drug User Fee Act (PDUFA): History, Reauthorization in 2007, and Effect on FDA*, by Susan Thaul.

⁴¹ FDCA §§ 739(8) and 739(9).

⁴² See "Antibiotic Measures That Were Axed From ADUFA May Still Be Included," *InsideHealthPolicy.com*, July 9, 2008.

⁴³ Antimicrobial resistance occurs when microbes—usually bacteria, though resistance can also be seen in viruses, fungi, and parasites—are able to resist the effects of antimicrobial drugs in stopping microbial growth and reproduction. Microbes have a number of mechanisms to resist antimicrobial drug effects. These mechanisms are often coded in microbial genes, may be transferred between microbes, and often proliferate when microbes are exposed to antimicrobial drugs. Antibiotics are a type of antimicrobial drug. For background, see the section "Antimicrobial Resistance," in CRS Report RL31853, *Food Safety Issues in the 109th Congress*, by Donna U. Vogt.

⁴⁴ FDA presents its rationale in its comments on a 2004 Government Accountability Office (GAO) report, "Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals," GAO-04-490, April 2004, pp. 88-94.

⁴⁵ FDA, "FDA Issues Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs to Help Prevent Creating New Resistant Bacteria," news release, October 23, 2003, at <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00964.html>.

A coalition of consumer groups opposed reauthorization of ADUFA, but in the event of its reauthorization, called for it to authorize the use of ADUFA funds for the following postmarket activities related to antimicrobial resistance: safety reviews of currently approved antimicrobial drugs, the collection of veterinary drug use data to support antimicrobial risk assessments, and enhanced surveillance for antimicrobial resistance related to animal drug use.⁴⁶

⁴⁶ See public comments of Brise Tencer, the Keep Antibiotics Working Coalition, ADUFA meeting transcript, and “Advocates Want Animal Drug User Fees Spent on Post-Market Safety,” *FDA Week*, April 18, 2008. Groups in the Coalition include Center for Science in the Public Interest, Food Animal Concerns Trust, Humane Society of the United States, and Union of Concerned Scientists, among others. The coalition’s comments of April 14, 2008, regarding ADUFA reauthorization are available at http://www.keepantibioticsworking.org/new/resources_library.cfm?RefID=102290.

Appendix A. Summary of Provisions in ADUFA I

Table A-I. Summary of Provisions in ADUFA I

| Provision | FFDCA Section | U.S.C. Section (Title 21) | Summary |
|---------------------------------------------|---------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Definitions | § 739 | § 379j-11 | Defines covered types of applications, sponsors, processes, allowable activities, and other matters. |
| Types of fees | § 740(a) | § 379j-12(a) | Requires the Secretary to collect animal drug user fees for applications, products, establishments, and product sponsors. Establishes requirements regarding payment, refunds, and exceptions. |
| Total fee revenues | § 740(b) | § 379j-12(b) | Establishes the <i>total revenues</i> (not the individual fees) that may be collected for each type of fee above, for each fiscal year from FY2004—FY2008. |
| Fee adjustments | § 740(c) | § 379j-12(c) | Requires the Secretary to make annual adjustments to total fee revenues based on inflation and workload. The workload adjustment shall not result in annual revenues lower than those authorized in subsection (b), adjusted for inflation. Requires the Secretary to establish annual fees 60 days prior to the start of each fiscal year, and publish final fees and methodology in the Federal Register. Authorizes the Secretary, if necessary for FY2008, to set revenues sufficient for up to three months of operating reserve, for carryover into the first three months of FY2009. Prohibits the Secretary from collecting total annual revenues that exceed total annual costs. |
| Fee waivers and reductions | § 740(d) | § 379j-12(d) | Requires the Secretary to grant fee waivers or reductions if he finds that (1) fees would hinder innovation; (2) fees would exceed review costs; (3) the application is solely for a minor reformulation of an approved drug for use in feed; (4) the application is solely for a minor use or minor species indication; or (5) the sponsor is a small business (an entity with fewer than 500 employees, including employees of affiliates) submitting its first animal drug application. Establishes additional requirements regarding the small business waiver. |
| Effect of failure to pay fees | § 740(e) | § 379j-12(e) | Establishes that for non-payment of fees after 30 days of their due date, pending applications, supplements and investigational animal drug submissions shall be considered incomplete, and the Secretary may discontinue their review. |
| Assessment of fees (one fee trigger) | § 740(f) | § 379j-12(f) | Prohibits the collection of fees unless FDA salaries and expenses for a given fiscal year, excluding fees, are at least equal to appropriations for FDA salaries and expenses for FY2003, excluding fees and multiplied by the applicable adjustment factor. Does not require the Secretary to modify assessed fees if this trigger is met part-way through a fiscal year. |
| Appropriations authority (two fee triggers) | § 740(g) | § 379j-12(g) | Authorizes the collection of fees only if authorized in advance in annual appropriations. Such amounts are available until expended. Authorizes the collection of fees only if FDA spends, for the review of animal drugs, at least as much as it spent for this purpose from appropriations in FY2003, adjusted for inflation, unless the amount is within specified limits. Authorizes appropriations for fees for FY2004—FY2008, and provides that fees collected in excess of annual amounts authorized may be carried over and subtracted from future fee authority. |
| Collection of unpaid fees | § 740(h) | § 379j-12(h) | Establishes that if assessed fees are not paid within 30 days after they are due, such fees shall be treated as a claim of the United States Government subject to 31 U.S.C. §§ 3711 et seq. |

| Provision | FFDCA Section | U.S.C. Section (Title 21) | Summary |
|---------------------------------------------------|---------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Waivers and reductions | § 740(i) | § 379j-12(i) | Requires that requests for consideration for fee waivers, reductions or refunds be submitted to the Secretary in writing not later than 180 days after such fee is due. |
| Rule of construction | § 740(j) | § 379j-12(j) | States that this section may not be construed to require that the number of full-time equivalent positions in HHS, for officers, employees, and advisory committees not engaged in the process of the review of animal drug applications, be reduced to offset the number of officers, employees, and advisory committees so engaged. |
| ANADAs (generic animal drugs) | § 740(k) | § 379j-12(k) | Requires the Secretary: (1) to the extent practicable, to segregate the review of ANADAs from the process for the review of NADAs; and (2) to adopt other administrative procedures to ensure that review times of ANADAs do not increase due to activities under the user fee program. |
| Reauthorization: consultation and recommendations | NA | § 379j-11 note | Requires the Secretary, in developing recommendations to Congress for reauthorization after FY2008, to consult with Congress and applicable stakeholder groups, publish recommendations in the Federal Register, hold a public meeting, and seek public comment. |
| Required reports | NA | § 379j-11 note | Requires the Secretary to report to Congress annually regarding program performance and funding. |
| Sunset provisions | NA | § 379j-11 note | Establishes that provisions in FFDCA § 740 shall not be in effect after October 1, 2008, and that provisions regarding reauthorization consultation and required reports shall not be in effect after 120 days after such date. |

Appendix B. The Animal Drug Approval Process⁴⁷

Like human drugs, animal drugs must be shown to be safe and effective before they can be marketed. The FDA Center for Veterinary Medicine (CVM), Office of New Animal Drug Evaluation (ONADE), is responsible for the premarket review of new animal drugs, and it grants approvals when requirements have been met. (CVM also regulates veterinary devices but does not require their premarket approval. Veterinary biologics are regulated by the U.S. Department of Agriculture.⁴⁸)

Specific statutory requirements for the approval of “new animal drugs” are found in the Federal Food, Drug, and Cosmetic Act (FFDCA), section 512 [21 U.S.C. § 360b]. Specific regulations are primarily at 21 C.F.R. 510, et seq. In each case, general provisions also apply, such as labeling requirements and enforcement provisions. According to CVM, virtually all animal drugs meet the FFDCA definition of “new animal drug.”⁴⁹ The term does not, as it may sound, distinguish between pioneer (i.e., brand-name) and generic animal drugs. Several application names and acronyms used in the animal drug approval process derive from the term “new animal drug.” These names and acronyms are described in **Table B-1** and discussed below. In this report, the terms “animal drug” and “new animal drug” are used interchangeably. Requirements for the approval of pioneer animal drugs begin at FFDCA section 512(b)(1), and those for the approval of generic animal drugs begin at FFDCA section 512(b)(2). The respective products are often referred to as “(b)(1)” or “(b)(2)” animal drugs.

⁴⁷ Information in this section is drawn from Carol J. Haley, “The Minor Use and Minor Species Animal Health Act: Past, Present and Future,” *Food and Drug Law Journal*, vol. 61, pp. 13-43, 2006 (hereafter referred to as Haley MUMS article), and Steven D. Vaughn, FDA/CVM “Overview of the Animal Drug Approval Process,” undated presentation, at <http://www.fda.gov/cvm/nadaappr.htm>.

⁴⁸ See FDA CVM, “How FDA Regulates Veterinary Devices,” May 2003, at <http://www.fda.gov/cvm/regofdevices.htm>. Veterinary biologics (e.g., vaccines and clinical laboratory tests) are regulated by the U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service, Center for Veterinary Biologics, at http://www.aphis.usda.gov/animal_health/vet_biologics/. For more information about CVM activities, see “Animal Drugs and Feeds” in CRS Report RL34334, *The Food and Drug Administration: Budget and Statutory History, FY1980-FY2007*, coordinated by Judith A. Johnson.

⁴⁹ “New animal drug” is defined at FFDCA § 201(v) [21 U.S.C. § 321(v)].

Table B-I. Terms Used in the Animal Drug Approval Process

| Term | Description |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Investigational New Animal Drug (INAD) | A pioneer animal drug for which a sponsor seeks approval pursuant to FFDCA section 512(b)(1). The term is commonly used to refer to the information file that is developed for review. |
| New Animal Drug Application (NADA) | Formal application to FDA for approval of a pioneer animal drug. Refers to the entire process. Review is typically conducted in stages. |
| Administrative NADA | The final step in applying to FDA for approval of a pioneer animal drug, in which summaries of stepwise reviews and other materials are presented. |
| Generic Investigational New Animal Drug (JINAD) | A generic animal drug for which a sponsor seeks approval pursuant to FFDCA section 512(b)(2). The term is commonly used to refer to the information file that is developed for review. |
| Abbreviated New Animal Drug Application (ANADA) | Formal application to FDA for approval of a generic animal drug. |
| Veterinary Master File (VMF) | A voluntary submission to FDA of confidential information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of animal drugs, which FDA may use in evaluating applications. Comparable to a Drug Master File (DMF) for human drugs. |
| Supplemental application | Filed by sponsors seeking changes in the conditions of an existing approved NADA or ANADA. Requested changes may be significant (e.g., a new species or indication) or routine (e.g., product manufacturing changes). |

The animal drug approval process is generally similar to that for human drugs, devices, and many biologics.⁵⁰ Animal drug sponsors conduct discovery research on drug candidates, including pilot studies of dose and potential toxicity. Sponsors seeking to develop a promising drug candidate (an Investigational New Animal Drug, or INAD) submit relevant information to CVM. Usually, the process begins with a sponsor's request for an exemption, pursuant to FFDCA section 512(j), to allow for the interstate shipment of the unapproved product in order that clinical trials of the drug's safety and effectiveness may be conducted. Sponsors wishing to begin the FDA approval process for an INAD submit a New Animal Drug Application (NADA) to CVM.

CVM generally conducts phased review of animal drugs, encouraging sponsors to submit information about a product as it becomes available, rather than all at once, and to maintain ongoing consultations with CVM about technical and other requirements. Technical requirements include (1) the demonstration of safety in the target species, as well as in the environment and in humans (including those handling and administering the drug, and those consuming the products of food-producing animals, if applicable); (2) the demonstration of effectiveness in the target species; and (3) matters regarding manufacturing methods, controls, and product stability.

When all required information is available, sponsors submit a final "Administrative NADA," containing agency sign-off letters for all phases of review, a labeling proposal, and other information. An approved NADA means the product is safe and effective for its intended use, and that the methods, facilities, and controls used for the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity. As with approved

⁵⁰ See "FDA Approval of New Drugs," in CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by Susan Thaul; "Background: FDA and Medical Device Regulation," in CRS Report RL34571, *Medical Device User Fees and User Fee Acts*, by Erin D. Williams; and "Regulatory Framework," in CRS Report RL34045, *FDA Regulation of Follow-On Biologics*, by Judith A. Johnson.

human drugs, sponsors of approved NADAs are required to notify FDA regarding an approved drug's postmarket performance, including any adverse events.

The animal drug approval process differs from the process for human products in two important ways. First, to support the requirement for demonstration of safety in humans, if an animal drug is intended for use in a food-producing animal, the sponsor must develop methods to test for drug residues in the human food product (e.g., meat, milk, eggs, honey). FDA determines whether the drug can be used safely in food-producing animals, with respect to public health. If approved, the drug's label must address a "withdrawal time" if necessary (i.e., a period of time that the drug must be withheld before an animal's products can be marketed for human consumption), allowing drug residues to fall below levels of concern.⁵¹

Second, although CVM requires clinical trials to demonstrate an animal drug's safety and effectiveness, these trials are, necessarily and as a matter of regulation, somewhat different from clinical trials required for the approval of human drugs. An approved animal drug may be labeled for use only in the species for which trials were conducted. However, veterinarians are permitted, under certain conditions, to use approved drugs for unapproved uses—so-called "extra-label" uses—such as use in species other than those on the label, or for indications other than those on the label.⁵² Also, clinical trials for animal drug approval need not be as extensive as trials for human drugs. Among other things, initial testing of the animal drug may begin in the target species, whereas candidate human drugs are studied to determine their safety in animals first, before human trials are begun.

CVM also has authority to approve generic animal drugs.⁵³ Sponsors seeking approval of a Generic Investigational New Animal Drug (JINAD) must submit an Abbreviated New Animal Drug Application (ANADA). The generic product and its uses must be the same as those of an approved animal drug, with certain exceptions, and it must be demonstrated that the generic product is bioequivalent to the approved product.⁵⁴ Holders of approved or pending NADAs must submit certain patent information to CVM. CVM publishes patent information on approved NADAs, and requires ANADA applicants to certify that their product would not infringe upon a current patent, or that any such current patent is invalid. Sponsors seeking to market a generic version of an approved animal drug for a substantially different use than that currently approved (such as a label indication for a new species) often must conduct clinical trials, and typically need an investigational exemption pursuant to FFDCA section 512(j) in order to ship the drug interstate.

Finally, CVM has authority for the conditional approval of drugs to treat minor animal species (e.g., fish) and uncommon diseases in major animal species. This allows sponsors to market a drug before collecting all necessary effectiveness data, but after proving that the drug is safe.⁵⁵

⁵¹ These levels are called *tolerances* and are established for each approved drug by FDA, using information submitted in the application, and from other sources.

⁵² P.L. 103-396, The Animal Medicinal Drug Use Clarification Act (AMDUCA), 1994. AMDUCA also authorized veterinarians to use approved human drugs in animals. Certain restrictions of extra-label use apply to the use of drugs in food-producing animals.

⁵³ P.L. 100-670, The Generic Animal Drug and Patent Term Restoration Act, 1988.

⁵⁴ See FDA/CVM information at <http://www.fda.gov/cvm/gadaptra.html>.

⁵⁵ P.L. 108-282, The Minor Use and Minor Species (MUMS) Animal Health Act, 2004. For more information on minor uses and minor species, see Haley MUMS article and FDA/CVM information at <http://www.fda.gov/cvm/minortoc.htm>.

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